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PROSTATE CANCER RISK IN U.S. BLACKS AND WHITES WITH A FAMILY HISTORY OF CANCER

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Prostate cancer occurs more frequently in U.S. blacks than whites. A population-based case-control study which investigated the association with family history of cancer was carried out among 981 men (479 black, 502 white) with pathologically confirmed prostate cancer, diagnosed between August 1, 1986, and April 30, 1989, and 1,315 controls (594 black, 721 white). Study subjects, aged 40–79, resided in Atlanta, Detroit, and 10 counties in New Jersey, geographic areas covered by population-based cancer registries. Prostate cancer risk was significantly elevated among those who reported a history of prostate cancer in first-degree relatives (O.R. = 3.2; 95% C.I.: 2.0–5.0), with blacks and whites having similarly elevated risks. These risks were unchanged by statistical adjustment for job-related socio-economic status, education, income, and marital status. Overall, the ORs associated with history of prostate cancer in fathers and brothers were 2.5 (95% C.I.: 1.5–4.2) and 5.3 (95% C.I.: 2.3–12.5), respectively. Risks associated with a family history of prostate cancer were consistently elevated among younger and older subjects. Only small non-significant excesses of prostate cancer risk were associated with a family history of breast, colorectal, or other cancers. While familial occurrence is a key risk factor for prostate cancer and likely to be genetically based, the similar familial risks among blacks and whites suggest that the ethnic disparity in incidence is influenced by environmental factors.

Based upon U.S. age-adjusted rates for 1990, prostate cancer is the most common form of cancer among U.S. black men (average incidence: 163 per 100,000 men), and a leading type of cancer among U.S. white men (128 per 100,000). Mortality from prostate cancer is more than 2 times as high among U.S. blacks (average mortality: 55 per 100,000 men) than whites (24 per 100,000) (Miller *et al.,* 1993). The extent to which this ethnic disparity is attributable to environmental or genetic factors is unknown.

The question of a familial or genetic component in prostate cancer risk has received limited study and few data are available to determine whether heritable factors contribute to the higher rates of prostate cancer among U.S. blacks than whites. We have carried out a large population-based study of this disease among U.S. blacks and whites and report here on the risks associated with family history of cancer.

MATERIAL AND METHODS

This case-control study of prostate cancer is one component of a multi-center study of cancers of the esophagus, pancreas, and prostate, and multiple myeloma among U.S. blacks and whites. Pacific Islanders, Asians, and native Americans were excluded due to small numbers. Study subjects resided in the geographic areas covered by the population-based cancer registries of the Georgia Center for Cancer Statistics (Fulton and DeKalb counties), the Metropolitan Detroit Cancer Surveillance System (Wayne, Oakland, and Macomb counties), and the 10 counties included in the cancer registry of the New Jersey State Health Department.

Cases were men aged 40–79 identified from pathology and outpatient records at hospitals covered by these registries, newly diagnosed with pathologically confirmed prostate cancer, between August 1, 1986, and April 30, 1989. Information on stage of prostate cancer was obtained from medical records. To ensure a broad distribution by ethnicity and age, we selected varying proportions of cases by random sampling for inclusion in the study from among the total number of cases identified in each age-ethnic group. The sampling frequency ranged from 100% for those younger than 55 to 20% for white males aged 65–74 and 17% for black males aged 65–74.

Population controls were selected in the 3 geographic areas, proportional to the expected age, sex, and ethnic distribution of the combined cases for the 4 cancer sites. Population controls below 65 years of age were selected at periodic intervals by random digit dialing (RDD) (Waksberg, 1978). Older controls were systematically selected (after a random start) from computerized records of the Health Care Financing Administration stratified by age (65–69, 70–74, 75–79), sex, and ethnicity (black, white), for each geographic area.

In-person interviews were conducted for the cases and controls, usually in the subject's home. Prostate cancer cases and male controls were questioned about a number of factors possibly related to prostate cancer, including demographics, occupational history, and family history of cancer. Questions were asked about the occurrence of cancer in first-degree blood relatives, including parents, siblings, and children. A socio-economic status score was derived from the reported usual occupation. Medical records of the cases were abstracted for diagnostic confirmation.

Odds ratios (O.R.) for prostate cancer were estimated by logistic regression analysis (Breslow and Day, 1980), with adjustment for age (40–49, 50–54, . . . 70–74, 75+), study site (Atlanta, Detroit, New Jersey), and, where appropriate, for ethnicity (black, white). In selected analyses, odds ratios were also adjusted for socio-economic status (low, middle, high), education (0–8 years, 9–12 years, at least some college), income (< $15,000, $15,000–34,999, $35,000 + per year), and marital status (never married, currently married, other).

In total, 1,292 cases and 1,767 controls were identified for study. Interviews were obtained for 988 cases (76%) and 1,336 controls (76%). After adjustment for non-response in the initial phase of screening for eligibility among RDD contacts, the response rate in controls was 70%. Six cases and 6 controls

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TABLE I – HISTORY OF PROSTATE CANCER, BY SELECTED CHARACTERISTICS, AMONG FIRST-DEGREE FAMILY MEMBERS OF POPULATION-BASED CONTROLS, ATLANTA, DETROIT, NEW JERSEY, 1986–1989

Characteristics	Population controls		
	Total	Family history	
	N	n	(%)
Ethnicity			
Black	583	9	(2)
White	711	21	(3)
Age			
40–59	541	10	(2)
60–69	398	13	(3)
70+	355	7	(2)
Income			
below $15,000	390	12	(3)
$15–35,000	435	6	(1)
$35,000+	371	11	(3)
Education			
0–8 years	300	9	(3)
9–11 years	225	3	(1)
12 years+	763	18	(2)
Marital status			
married	950	24	(3)
never married	56	1	(2)
other	288	5	(2)
Socio-economic status			
low	579	9	(2)
moderate	523	14	(3)
high	187	7	(4)
Total[1]	1,294	30	(2)

[1]Twenty-one controls (11 black, 10 white) did not provide information on family history of cancer.

were dropped from the analysis due to incomplete interviews. Sixteen subjects (15 controls, 1 case) were excluded because of a prior history of prostate cancer. The final study group consisted of 981 cases (479 black, 502 white) and 1,315 controls (594 black, 721 white). Nine cases (0.9%) and 21 controls (1.6%) did not provide a response about family history of prostate cancer.

RESULTS

Sixty-seven cases (7%) and thirty controls (2%) reported a history of prostate cancer in a first-degree relative (O.R. = 3.2, 95% CI: 2.0–5.0). The prevalence of familial prostate cancer was slightly lower among black (2%) than white (3%) controls, and did not show substantial variation by other selected factors (Table I). As shown in Table II, prostate cancer risks were significantly elevated among both blacks (O.R. = 3.4; 95% C.I.: 1.5–7.5) and whites (O.R. = 3.1; 95% C.I.: 1.8–5.3). The O.R. associated with paternal history of prostate cancer (42 cases, 24 controls) was 2.5 (95% C.I.: 1.5–4.2), while the O.R. associated with prostate cancer in a brother (28 cases, 7 controls) was 5.3 (95% C.I.: 2.3–12.5). Only one control and no cases reported prostate cancer in a son. The familial risk for prostate cancer was unchanged by statistical adjustment for socio-economic status, based upon usual occupation, education, income, and marital status. When risks were examined within categories of these variables for blacks and whites combined, the excesses remained except for some decline in subjects with low family income (<$15,000, O.R. = 1.6; 95% C.I.: 0.7–3.4) or limited education (less than 9 years, O.R. = 1.8; 95% C.I.: 0.7–4.5). Risk was similar for localized ($O.R._{blacks}$ = 3.1, 95% C.I.: 1.3–7.5; $O.R._{whites}$ = 3.2, 95% C.I.: 1.7–5.9) and regional or distant disease ($O.R._{blacks}$ = 3.4, 95% C.I.: 1.3–9.3; $O.R._{whites}$ = 2.1, 95% C.I.: 0.9–4.5).

Risks associated with a family history of prostate cancer were elevated in each age group: 40–59 (O.R. = 4.1; 95% C.I.: 1.8–9.3), 60–69 (O.R. = 2.4; 95% C.I.: 1.2–4.8), and 70 years or older (O.R.: 3.6; 95% C.I.: 1.5–8.6) (Table III). The age-specific risks for prostate cancer associated with a family history of prostate cancer were unchanged by statistical adjustment for socio-economic status, education, income, and marital status.

Small and non-significant increases in risk were associated with history of breast cancer in female relatives (O.R. = 1.3; 95% C.I.: 0.9–1.9), and of colorectal (O.R. = 1.2; 95% C.I.: 0.8–1.8) and other cancers (O.R. = 1.2; 95% C.I.: 1.0–1.5) in all relatives. These risks were similar for blacks and whites, except that the increased risk associated with a family history of colorectal cancer was seen only in blacks (Table II). The O.R. associated with a history of maternal breast cancer was 1.0 (95% C.I. = 0.6–1.7), while the O.R. associated with breast cancer in a sister was 1.8 (95% C.I.: 1.1–3.0). Risks were

TABLE II – PROSTATE CANCER RISK BY HISTORY OF CANCER AMONG PARENTS, SIBLINGS, AND CHILDREN, ATLANTA, DETROIT, NEW JERSEY, 1986–1989

	Family history of cancer							
	Prostate		Breast		Colon		Other	
	No	Yes	No	Yes	No	Yes	No	Yes
Blacks								
Case	448	24	448	24	456	16	372	100
Control	574	9	561	22	570	13	479	104
O.R.[1]	3.4		1.3		1.8		1.3	
C.I.	1.5–7.5		0.7–2.4		0.8–3.9		0.9–1.8	
Whites								
Case	457	43	461	39	469	31	327	173
Control	690	21	668	43	669	42	493	218
O.R.[1]	3.1		1.3		1.0		1.2	
C.I.	1.8–5.3		0.8–2.0		0.6–1.7		0.9–1.5	
All								
Case	905	67	909	63	925	47	699	273
Control	1264	30	1299	65	1239	55	972	322
O.R.[2]	3.2		1.3		1.2		1.2	
C.I.	1.0–5.0		0.9–1.9		0.8–1.8		1.0–1.5	

[1]Odds ratio (O.R.) adjusted for age and study site.–[2]Odds ratio (O.R.) adjusted for age, ethnicity, and study site.

TABLE III – PROSTATE CANCER RISK BY HISTORY OF PROSTATE CANCER AMONG MALE FAMILY MEMBERS, ATLANTA, DETROIT, NEW JERSEY, 1986–1989, BY AGE OF STUDY SUBJECTS

	Family history of prostate cancer	
	No	Yes
Age 40–59		
Case	265	20
Control	531	10
O.R.[1]	4.1	
C.I.	1.8–9.3	
Age 60–69		
Case	313	24
Control	385	13
O.R.[1]	2.4	
C.I.	1.2–4.8	
Age 70+		
Case	327	23
Control	348	7
O.R.[1]	3.6	
C.I.	1.5–8.6	

[1]Odds ratio (O.R.) adjusted for age (within age groupings), ethnicity, and study site.

similar for parental (O.R. = 1.2; 95% C.I.: 0.7–1.9) or sib (O.R. = 1.1; 95% C.I.: 0.5–2.2) occurrence of colorectal cancer, and for parental (O.R. = 1.1; 95% C.I.: 0.9–1.4) or sib (O.R. = 1.3; 95% C.I.: 1.0–1.7) occurrence of other cancers.

In addition, some increases in risk were associated with a family history of lung cancer (O.R. = 1.3; 95% C.I.: 0.9–1.8) both in blacks (O.R. = 1.2; 95% C.I.: 0.6–2.3) and whites (O.R. = 1.3; 95% C.I.: 0.8–2.1). Risk was also elevated among whites with a family history of uterine cancer (O.R. = 2.5; 95% C.I.: 1.0–5.9), but not among blacks (O.R. = 0.9; 95% C.I.: 0.4–2.3). Several other tumor sites were considered for blacks and whites combined, as the numbers were too few for ethnicity-specific analyses. Non-significant excesses in risk were noted among those with a family history of multiple myeloma (O.R. = 1.7; 95% C.I.: 0.4–7.8) and leukemia (O.R. = 1.6; 95% C.I.: 0.9–2.9). No increased risk was associated with occurrence of brain cancer or lymphoma in relatives.

DISCUSSION

In our population-based case-control study, a 3-fold excess risk of prostate cancer was associated with a history of prostate cancer in a first-degree relative. Since the lower bound of the risk estimate (95% confidence interval) was 2.0, it is unlikely that this finding is due to chance ($p < .001$). Except for advancing age, risks of this magnitude have not been determined for any other putative risk factor for prostate cancer. Although such familial associations may be due to environmental factors shared in the household, the level of risk (3-fold) and the lack of any potent environmental factors defined for prostate cancer suggest that genetic determinants are involved.

This study was designed to determine reasons for the greater frequency of occurrence of prostate cancer among U.S. blacks as compared to whites. The risk associated with a familial history of prostate cancer was similar among both groups, suggesting that genetic susceptibility does not account for the ethnic disparity in risk. The familial risks estimated by our study generally agree with those of other interview studies among whites (Steele *et al.,* 1971; Krain, 1974; Meikle and Stanish, 1982; Schuman *et al.,* 1977; Kolonel *et al.,* 1988; Honda *et al.,* 1988; Ghadirian *et al.,* 1991; Steinberg *et al.,* 1990; West *et al.,* 1991; Spitz *et al.,* 1991) and with the one study among U.S. blacks (Jackson *et al.,* 1980). Studies which relied upon record linkage of familial cancer mortality and incidence reports also showed similarly increased risks (Woolf, 1960; Holloway and Sofaer, 1992; Cannon-Albright *et al.,* 1994). Thus, numerous studies of varying design have consistently revealed an increased risk of prostate cancer associated with a family history of this disease. We saw no evidence that the magnitude of the familial risk varied significantly by age at diagnosis. Stronger associations have been noted among younger men in some (Carter *et al.,* 1992) but not other (Cannon-Albright *et al.,* 1994) studies.

In addition to the familial tendency to prostate cancer, we found weaker evidence that prostate cancer risk was associated with familial occurrence of breast cancer (particularly in sisters), uterine cancer (in whites only), colorectal cancer, multiple myeloma, and leukemia. Several studies have suggested that prostate cancer tends to aggregate in families with cancers of the breast, ovaries, and endometrium (Thiessen, 1974; Anderson and Badzioch, 1992, 1993; Tulinius *et al.,* 1992; Carter *et al.,* 1993), possibly due to the *BRCA1* gene located on chromosome 17q (Arason *et al.,* 1993; Ford *et al.,* 1994).

Prostate cancer has also occasionally been observed in families with Li-Fraumeni syndrome, in which young people are prone to diverse cancers including breast cancer, sarcomas, leukemia, brain tumors, and adrenocortical neoplasms (Li *et al.,* 1988) due to germline alterations in *p53* (Malkin *et al.,* 1990). In our study, small increases in prostate cancer risk were associated with a familial occurrence involving some of these neoplasms (*i.e.,* breast cancer, leukemia). Although it is not clear that risk of prostate cancer is increased in the Li-Fraumeni syndrome, it is noteworthy that somatic *p53* mutations occur frequently in prostate cancer (Chi *et al.,* 1994).

Our study has certain limitations that should be discussed. Because of the interest in a number of potential risk factors for prostate cancer and the need to limit the duration of the interview, we did not collect information on the number of relatives at risk of cancer, their ages, or level of certainty about their disease status. Also, cancer history in family members was not verified, nor are the circumstances leading to a diagnosis of cancer in a family member known. Verification of reported family history of cancer (Love *et al.,* 1985) and specifically prostate cancer (Steinberg *et al.,* 1990) has been shown to be good (true positives), but no study has evaluated the impact of failure to report familial cases (false negatives). Given the reported incidence of this disease in the United States and its greater frequency in U.S. blacks, we thought it surprising that only 3% of white controls and 2% of black controls reported a family history of prostate cancer. Other recent studies, however, have shown similar results (Kolonel *et al.,* 1988; Ghadirian *et al.,* 1991; West *et al.,* 1991). Without detailed data on family structure and respondent knowledge of family disease history it is not possible to estimate the extent of under-reporting in black and white study subjects. Also, knowledge of a positive family history of prostate cancer could result in an ascertainment bias for prostate cancer, but our analysis showed similar results for localized and advanced or regional disease.

The precision of reporting of family history is likely to be greater for cases than controls, but record-based studies (Woolf, 1960; Holloway and Sofaer, 1992; Cannon-Albright *et al.,* 1994) show similar results suggesting that the finding of a familial risk for prostate cancer is not due to this potential bias. We did not find substantial differences in the reporting of family history of prostate cancer by several demographic characteristics, but familial risk estimates were somewhat lower in subjects with limited income or education who may be less informed about their family history of disease. Risk estimates for blacks and whites could be differentially biased but statistical adjustment for these factors did not substantially change the overall or ethnicity-specific estimates.

In summary, a genetic component to prostate cancer is suggested by the familial tendency to prostate cancer observed in our case-control study. Since familial risks were similarly elevated in U.S. blacks and whites, the ethnic disparity in prostate cancer occurrence likely has important environmental or behavioral determinants. The genetic mechanisms underlying the familial susceptibility to prostate cancer, and the interaction with environmental and hormonal factors, warrant further study.

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